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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,022	03/08/2007	Tadao Saito	SPO-124	5950

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
02/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,022	SAITO ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-21* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-7 and 10-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTO-90C, Revised Notice*.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10561022	3/8/07	SAITO ET AL.	SPO-124

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EXAMINER	
ZACHARY C. HOWARD	
ART UNIT	**PAPER**
1646	20090126

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

In particular, there are sequences in each of Figure 1, 2, 3, 4, 6, 7, 8 and 9 that are not identified by Sequence Identifier (SEQ ID NO:) in either the Figure itself or the Brief Description of the Figure in the Specification.

M.P.E.P. 2422.02 states: "It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO: X") must be used, either in the drawing or in the Brief Description of the Drawings."

The instant specification (or the drawings themselves) will need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence.

APPLICANT IS GIVEN THREE MONTHS FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R.. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

The addresses below are effective 5 June 2004. Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Web (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual - ePAVE)
2. Mailed to:

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Alexandria, VA 22313 1450
3. Hand Carry, Federal Express, United Parcel Service or other delivery service to:
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

PTO-90C (Rev.04-03)

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-7 and 10-21 are pending in the instant application.

Election/Restrictions

Applicants' election of Group I, claims 1-7 and 12-15, in the reply filed on 4/28/08 is acknowledged. Applicants do not indicate whether the election is with or without traverse, but because Applicants did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 10, 11 and 16-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the 4/28/08 reply.

Claims 1-7 and 12-15 are under consideration.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in each of Figures 1, 2, 3, 4, 6, 7, 8 and 9 are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Please see attached PTO-90C and Revised Notice to Comply

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation “the test microorganism” in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Claim 6 depends from claim 5, which recites "selecting from the plurality of test microorganisms those assessed to activate the intestinal tract immune system". The use of "those" indicates that more than one microorganism is selected (i.e., plural). Thus, the antecedent basis of "the microorganism" (singular) in dependent claim 6 is indefinite because it is unclear which of the microorganisms of claim 5 is now being referred to in the singular.

Claim 7 depends from claim 6 and also recites "the microorganism" in line 1 and "bacterium" in line 2. There is insufficient antecedent basis for these limitations in the claim, for the same reason as claim 6 (i.e., because parent claim 5 tests and selects "test microorganisms" in the plural, but the recitations of "the microorganism" and "bacterium" are in the singular).

Furthermore, claim 7 is also indefinite because the specific antecedent basis of "the microorganism" is not clear. The recitation "microorganism" does not distinguish between the "test microorganisms" and the "those assessed to activate" (as recited in claims 5 and 6). Each genus differs in scope and it is not clear which is referred to in claim 7 by the recitation of "the microorganism". For purposes of prosecution, the claim is interpreted broadly to encompass either possibility.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention of independent claim 1 is a method of assessing whether a test sample activates the intestinal tract immune system, comprising (a) contacting a test sample with a cell expressing an intestinal tract tissue-expressed Toll-like receptor (TLR); and (b) measuring activity of the TLR using signal transduction in the cell as indicator, wherein the test is judged to be activating the intestinal tact immune system if the activity of the Toll-like receptor is increased as compared to activity of the Toll-like receptor in a cell not contacted with test sample. Claims 2-7 and 12-15 depend from claim 1 and limit the method to particular embodiments.

The claims recite the intended use of "for assessing whether a test sample activates the intestinal tract immune system". Thus, for purposes of enablement, the specification must enable the skilled artisan to practice the claimed method such that it results in assessment of intestinal tract immune system activation in response to a test sample.

The specification provides the following working examples in support of the claimed invention. Example 1 (pg 19) describes the cloning of swine TLR9 gene (SEQ ID NO: 1), which encodes the protein of SEQ ID NO: 2, and further provides a homology comparison with the human, mouse and cat TLR9 nucleic and amino acid sequences (SEQ ID NO: 3-8; known in the prior art). Example 2 (pg 19) describes the expression of swine TLR9 (sTLR9) as a transfectant in human HEK293T cells. Example 3 (pg 19) describes an "analysis of CpG DNA uptake", reporting that "while no significant difference was observed … in the uptake of different CpG DNAs ... [sTLR9]

incorporated relatively larger amounts of human CpG2006 than mouse CpG1826". The "human" and "mouse" CpG sequences are bacterial sequences that are specific for human and mouse TLR9. Example 4 (pg 20-21) describes an analysis of "swine TLR9 mRNA expression in different tissues" using real-time PCR and showing that sTLR9 "was strongly expressed in the intestinal lymphoid tissue, especially in the Peyer's patch and mesenteric lymph node" (pg 20).

The specification discusses these results in context of the prior art. The specification states that the prior art recognizes ten types of TLRs in humans, each recognizing a different molecular structure, and that TLR9 "recognizes bacterial DNA, in particular the CpG motif" (pg 1). The specification teaches that "certain DNA motifs derived from dairy lactic acid bacteria, including probiotic lactobacilli, can exhibit immuno potentiation of the intestinal tract immune system" (pg 2). The specification teaches that TLR9 "which is involved in activation of immune response, has been known to be strongly expressed in the spleen … [the] inventors have discovered for the first time that TLR9 is expressed in intestinal lymphoid tissues, in particular Peyer's patch and mesenteric lymph nodes" (pg 5). These tissues are "aggregative compositions" that are part of the gut-associated lymphoid tissues (GALT; pg 6). Antigens are taken up by cells in these regions and come into contact with antigen presenting cells (APCs) including dendritic cells and macrophages (pg 6).

Based on the working examples and other teachings, the instant specification asserts a connection between activation of TLR9-dependent signaling in a cell expressing TLR9 in response to a "test sample" (e.g., ligand) and activation of the "intestinal tract immune system". The specification asserts that activating compounds can be "used as samples having an immunostimulatory function in the treatment or prevention of diseases, for example, allergies, cancers, and infections" (pg 11). A preferred embodiment of the invention involves "assessing whether a test microorganism activates the intestinal tract immune system". In a preferred embodiment, the microorganism is a lactic acid bacterium (LAB).

However, the relevant art teaches TLR9 is not essential for IL-12 induction by lactic acid bacteria (LAB; Ichikawa et al, 2007. Biosci Biotechnol Biochem. 71(12):

3026-3032). IL-12 is produced by antigen-presenting cells as part of the innate immune response induced by LAB. Ichikawa et al caution that previous studies indicating a role for CpG DNA from LAB as activating innate immunity were performed with purified microbial components rather than whole organisms (paragraph bridging pages 3026-3027). Ichikawa et al teach that "[u]nexpectedly, no loss of recognition or cytokine induction was apparent in TLR2-, 4- or 9-deficient mice stimulated by KW3110 or any other immunomodulating LAB" (pg 3027). Thus, Ichikawa provides evidence that LAB activate the intestinal immune system by TLR9-independent mechanisms. This result casts considerable doubt onto the predictability of the association (as asserted by Applicants) between the activation of TLR9 in a cell-based assay and the activation of the "intestinal immune system", in particular by LAB which is a preferred embodiment of the claimed method (e.g., in dependent claim 7). Furthermore, Ichikawa report the same results with TLR2 and TRL4, extending the unpredictability to other members of the TLR family of receptors. The evidence indicates that expression of a TLR receptor in intestinal lymphoid tissue is not sufficient to predict that said receptor actually functions in activation of the intestinal immune system. Furthermore, even as of 2008, the relevant art reports that although "the expression of TLRs in the gastrointestinal tract has been examined, expression, localization and function of individual TLRs remain unclear" (pg 235 of Fukata et al, 2008. Oncogene. 27: 234-243). Thus, based on this evidence, the skilled artisan at the time of filing could not accurately predict whether or not activation of TLR9 or another TLR in said screening assays would actually result in activation of the "intestinal immune system". The skilled artisan would need to engage in undue experimentation to establish a reasonable correlation between activation of each TLR in cell-based assays and activation of "intestinal immune system". This would involve practicing the method steps of the claimed invention, but then further establishing an association between the samples that activate the receptor and those that activate the "intestinal immune system" in particular (including distinguishing those samples that activate the "immune system" in general from those that specifically activate the "intestinal immune system"). Essentially, the specification invites the skilled artisan to engage in experimentation to determine whether or not an association exists

at all. Such experimentation is undue, particularly because the teachings of Fukata et al suggest that even after performing such experimentation the results will in demonstrate that there is no such association.

Furthermore, in view that the method of screening lacks enablement for assessing whether a test sample activates the "intestinal immune system", the claims also lack enablement for "producing a pharmaceutical composition" (as recited in claim 3), because identifying a sample that activates the receptor does not reasonably correlate with a "pharmaceutical" (i.e., *in vivo*) use for the sample.

Furthermore, even if the claims were enabled with respect to a naturally-occurring mammalian TLR, such as the swine or human TLR9 sequences taught by the specification (SEQ ID NO: 2 and 4), the specification does not provide enablement for the vast genus of variants encompassed the claims. The specification specifically contemplates hybridizing sequences encoding proteins with at least 60% homology to SEQ ID NO: 2, 4, 6 or 8 (¶ 70 of the published application). Thus, the claims encompass mutant TLRs with hundreds of mutations in combination, e.g. 412 amino acid substitutions in SEQ ID NO: 2 (1030 aa). The specification also teaches that "[t]he present invention encompasses proteins comprising an amino acid sequence with one or more amino acid mutations in the amino acid sequence shown in SEQ ID NO: 2, 4, 6 or 8. Such amino acid mutations can occur naturally. The number of amino acid mutations is typically 30 amino acids or less, preferably 15 amino acids or less, more preferably 5 amino acids or less, and still more preferably 2 amino acids or less" (¶ 71 of the published application). While 30 amino acids of SEQ ID NO: 2 (1030 aa) represents only 3% of the protein, this is merely an exemplary and no actual limitation is placed on the number mutations present (i.e., "one or more…" is unlimited).

Thus, the claims encompass TLRs in which one or more amino acids of a naturally-occurring TLR (e.g., SEQ ID NO: 2) are substituted, deleted, and/or inserted. None of the claims include the limitation that the TLRs exhibit a functional characteristic of the parent polypeptide (e.g., SEQ ID NO: 2). Applicants do not disclose any actual or prophetic examples on expected performance parameters of any mutant receptors. The specification has not provided a working example of the use of a variant of a TLR, nor

sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids could be modified so as to produce a mutant TLR that retains a characteristic of the parent polypeptide. Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between a mutant TLR and its naturally-occurring form. If a variant of the protein is to have a similar structure and function similar to the naturally-occurring protein, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function. Conversely, if a protein variant need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al*. (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133].

Due to the large quantity of experimentation necessary to generate the large number of recited variants and screen them for activity, the lack of direction/guidance presented in the specification regarding which structural features are required for activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, each of claims 1-7 and 12-15 is directed to methods of using a broad genus of cells exogenously expressing TLRs. Specifically, the claimed encompass methods of screening using "isolated" cells (e.g. *in vitro* culture) and methods of screening using "non-isolated cells" (e.g., in a transgenic organism).

(1) Making and using isolated host cells in culture expressing the encoded receptor for use in screening is enabled. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells for this purpose.

Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

(2) The claims also encompass methods of *in vivo* screening wherein cells in an organism are genetically engineered to express a TLR (e.g. a transgenic organism). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells that can contribute to the germ line of any non-human mammal other than a mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing a TLR, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this portion of the rejection could be overcome by amending the claims to recite, for example, "…an isolated cell…" because such an amendment would clarify that the claims are directed only to host cells that are to be made and used in culture as described in context (1) above.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-7 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claims 1-7 and 12-15 are genus claims because the claims are directed to variant polypeptides, and cells comprising said variant polypeptides. Each genus is highly variant because a significant number of structural differences between genus members are permitted. First, the claims encompass method of use of any naturally-occurring mammalian Toll-like receptor (TLR), including each of TLR1-10. Second, as described above, the specification specifically contemplates hybridizing sequences encoding proteins with at least 60% homology to SEQ ID NO: 2, 4, 6 or 8 (¶ 70 of the published application). Thus, the claims encompass mutant TLRs with hundreds of mutations, e.g. 412 amino acid substitutions in SEQ ID NO: 2 (1030 aa). The specification also teaches that "[t]he present invention encompasses proteins comprising an amino acid sequence with one or more amino acid mutations in the amino acid sequence shown in SEQ ID NO: 2, 4, 6 or 8. Such amino acid mutations can occur naturally. The number of amino acid mutations is typically 30 amino acids or less, preferably 15 amino acids or less, more preferably 5 amino acids or less, and still more preferably 2 amino acids or less" (¶ 71 of the published application). While 30 amino acids of SEQ ID NO: 2 (1030 aa) represents only 3% of the protein, this is teaching is

merely exemplary and no actual limitation is placed on the number mutations present in the protein (i.e., "one or more…" is unlimited).

Furthermore, because the claims are directed to a method that comprises measuring "the activity of the Toll-like receptor using signal transduction in the cell as an indicator", the claims implicitly require that the recited TLR is functional active in cell-based signal transduction.

From the specification, it is clear that Applicants has possession of an isolated swine TLR9 polypeptide of SEQ ID NO: 2 that is expressed in "intestinal-tract tissue" and is functional in signal transduction. Furthermore, the specification discloses the human, cat and mouse TLR9 polypeptides known in the prior art (SEQ ID NO: 4, 6 and 8). Furthermore, numerous other naturally-occurring mammalian TLR receptor sequences are known in the prior art (TLR1-8 and 10). Ligands have been identified for each of the naturally-occurring mammalian TLR1-9 sequences (the ligand for TLR10 remains unknown), demonstrating that these sequences are functionally active when expressed in a cell.

The instant specification asserts that each of TLR1-10 are encompassed by "intestinal-tract tissue-expressed TLR" (¶ 61 of the published application), but provides no working examples in support of this assertion for TLR other than TLR9. However, the prior art provides evidence of TLR1-5, 7, 9 and 10 as also being expressed in the small intestine (Figure 1 of Zarember et al, 2002. The Journal of Immunology. 168: 554-561). The expression of TLR6 and 8 in the small intestine was not determined. Thus, one of skill in the art would reasonably conclude that the disclosure provide a representative number of species to describe the genus of "intestinal tract tissue-expressed Toll-like receptor" with respect to naturally-occurring mammalian sequences that would be active in a cell-based assay.

However, the specification fails to describe or teach any mutant TLR which differs from a naturally-occurring sequence and retains the cell-based activity of the parent polypeptide. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying

characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of TLR polypeptides. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish functional TLR mutants in the genus from non-functional TLR mutants are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the TLR polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed” (pg 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides,

and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods comprising (a) contacting a test sample with a cell expressing a naturally-occurring mammalian sequence of an intestinal-tract tissue-expressed Toll-like receptor and (b) measuring the activity of said Toll-like receptor using signal transduction in the cell as an indicator, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 12, 13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Akira et al, WO 02/06482 (published January 24, 2002; reference F2 on the 7/27/06 IDS (no translation provided)). The '482 publication of Akira et al is in Japanese; however, this reference is a publication of PCT/JP01/04731 and therefore an identical disclosure in English can be found in Akira et al, U.S. Patent Application Publication 20030124655 (reference U1 on the 7/25/05 IDS), which is a 371 of the same PCT. Thus, the paragraphs referenced below refer to the '655 publication.

In claim 1, the recitation of “for assessing whether a test sample activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art.

Furthermore, the concluding statement of claim 1 recites that the "the test sample is judged to be activating the intestinal tact immune system if the activity of the Toll-like receptor is increased as compared to activity of the Toll-like receptor in a cell not contacted with test sample". In other words, if the activity of the Toll-like receptor (TLR) is increased as compared to a control cell (not contacted with the test sample), then the test sample is judged to be activating the intestinal tract immune system. The "judgment" is a purely mental determination that relates only to the intended use and is therefore inherently met by any test sample that increases the activity of the TLR as compared to a control cell. In other words, this "judgment" does not result in any manipulative difference that patentably distinguishes the instant screening method from prior art screening methods wherein test samples that activate a TLR are identified. Every sample identified as activating a TLR receptor in a prior art method would also be "judged" to be activating the intestinal tract immune system by the instant method.

The recitation of a "cell expressing an intestinal tract tissue-expressed Toll-like receptor" broadly encompasses non-intestinal tract tissue cells that express (naturally or artificially/recombinantly) a Toll-like receptor (TLR) that is also naturally expressed in the intestinal tract tissue. The instant specification teaches that each of TLR1-10 are encompassed by the term "intestinal tract tissue-expressed TLR" (¶ 61 of the published application). Furthermore, the art provides evidence that the Toll-like receptor 9 (TLR9) is inherently expressed in intestinal tract tissue. Specifically, Zarember et al (2002; Journal of Immunology. 168: 554-561) teaches that human TLR9 is naturally expressed in the small intestine (Figure 1 on page 557), and Shimosato et al (2003. Biochimica et Biophysica Acta et al. 1627: 56-61) teach that porcine TLR9 (sTLR9) is expressed in several intestinal tissues, including duodenum, jejunum, ileum, Peyer's patches and mesenteric lymph nodes (Figure 3 on page 60). Thus, it is clear that TLR9 is inherently an "intestinal tract tissue-expressed" TLR.

As such, claim 1 encompasses a method comprising the steps of (a) contacting a test sample with a cell expressing a TLR9, and (b) measuring activity of the TLR9 using signal transduction in the cell as an indicator, and wherein a compound is identified by the method if it increases activity of the Toll-like receptor as compared to the activity of the Toll-like receptor in a cell not contacted with the test sample.

Akira et al teach that "a screening method for an agonist or an antagonist of a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence comprising steps of: in vitro culturing a cell expressing a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence in the presence of a target substance, and measuring/evaluating TLR9 activity" (¶ 15). Akira teach that the receptor protein recognizing bacterial DNA with unmethylated CpG is exemplified by human-derived TLR9 (SEQ ID NO: 2; ¶ 29). Akira et al further teaches that signal transduction of TLR9 by unmethylated CpG results in IL-12 production. Akira also teaches that the TLR9 activity is evaluated by comparison to cells not contacted with the test sample; for example, in the results of Figure 7, the activity induced in response to CpG is compared to medium alone (in which CpG is absent). Thus, Akira et al teach a method comprising the steps of (a) contacting a test sample (e.g., target substance) with a cell expressing a TLR9, and (b) measuring activity of the TLR9 using signal transduction in the cell as an indicator (e.g., IL-12 production), and wherein a compound is identified by the method if it increases activity (e.g., is an agonist) of TLR9 as compared to the activity of TLR9 in a cell not contacted with the test sample (e.g., in medium alone). Thus, the teachings of Akira et al anticipate claim 1.

Claim 2 depends from claim 1. In claim 2, the recitation of “wherein said method is used to screen for a sample that activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. The step of "(b) selecting from the plurality of test samples those assessed to activate the intestinal tract immune system" is inherently met by selecting any test sample that increases the activity of the Toll-like receptor as compared to a control cell, for the same reasons as for the conclusory statement of claim 1 (described above).

As such, claim 2 encompasses a method comprising (a) assessing whether a plurality of test samples activate the intestinal tract immune system by the assessment method of claim 1, and (b) selecting from the plurality of test samples those assessed to increase the activity of the receptor as compared to a control cell.

The teachings of Akira et al also meet all of limitations the method of claim 2, including that a plurality of test samples are subject to the assessment of claim 1. As described above, Akira et al teach using "test substances" (in the plural). Furthermore, as described above, Akira et al teach selection of agonists and selection in comparison to a control medium lacking the test substance. Thus, Akira et al teach selecting a ligand based on an increase an activity as compared to a cell not contacted with a test sample. Thus, the teachings of Akira et al also anticipate claim 2.

Claim 3 depends from claim 2. In claim 3, the recitation of “for producing a pharmaceutical composition that activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art.

As such, claim 3 encompasses a method comprising the steps of claim 2 and the further step of mixing the sample assessed to activate the receptor with a pharmaceutically acceptable carrier.

Akira et al further teach (¶ 16) that the invention includes a pharmaceutical composition comprising an agonist identified by the screening method described above. Akira et al further teach (¶ 57) that such compositions can be "any one as long as it … comprises an agonist or an antagonist of the receptor protein". No limiting definition of term "pharmaceutically acceptable carrier" is provided in the instant specification. Thus, a pharmaceutical composition taught by Akira et al would inherently comprise a "pharmaceutically acceptable carrier" because any component of the composition (even the agonist itself, if present alone in the composition) could be considered to be encompassed by the term "carrier". Thus, the teachings of Akira et al also anticipate claim 3.

Claim 4 depends from claim 1 and limits the method to one wherein the test sample is an extract from a test microorganism. In claim 4, the recitation of “used to

assess whether a test microorganism activates the intestinal tract immune system" in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Furthermore, similar to claim 1 (as described above), the concluding statement of claim 4 contains a "judgment" that is a purely mental determination that relates only to the intended use and is therefore inherently met by any test microorganism with an extract that increases the activity of the TLR as compared to a control cell. In other words, this "judgment" does not result in any manipulative difference that patentably distinguishes the instant screening method from prior art screening methods wherein an extract from a test microorganism that activates a TLR is identified. Every test microorganism with an extract identified as activating a TLR receptor in a prior art method would also be "judged" to be activating the intestinal tract immune system by the instant method.

Akira et al further teaches that "bacterial DNA comprising an unmethylated CpG sequence" can be derived from a variety of species (e.g., *E. coli*). Akira et al further teaches that bacterial DNA having an unmethylated CpG sequence can be used in the screening methods for agonists (¶ 54, last sentence). Thus, the teachings of Akira et al also anticipate claim 4.

Claim 5 depends from claim 4 and limits the method to one comprising assessing a plurality of test microorganisms. As with claim 4, the recitation of "used to screen for a microorganism that activates the intestinal tract immune system" in the preamble of claim 5 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Furthermore, as with claim 4, any microorganism with an extract that activates a Toll-like receptor is inherently assessed to be a microorganism that "activates the intestinal tract immune system".

As described above for claim 2, Akira et al teach the use of a plurality of test samples, and as described above for claim 4, Akira et al teach use of bacterial DNA in the methods of screening test substances. Thus, the teachings of Akira et al also anticipate claim 5.

Claim 12 depends from claim 1 and limits the "intestinal tract tissue" to "intestinal lymphoid tissue". The only recitation of "intestinal tract tissue" in claim 1 is lines 3-4,

which recite "...expressing an intestinal tract tissue-expressed Toll like receptor". Thus, claim 12 limits claim 1 to one wherein step (a) is "(a) contacting a test sample with a cell expressing an intestinal lymphoid tissue-expressed Toll-like receptor". As described above for claim 1, the art (Zarember et al, 2002) teaches that TLR9 is inherently expressed in intestinal lymphoid tissue. Thus, the teachings of Akira et al anticipate claim 12 for the same reason as claim 1.

Claim 13 depends from claim 12 and limits "intestinal lymphoid tissue" to "Peyer's patch or intestinal lymph node". Thus, claim 13 limits claim 12 to one wherein step (a) is "(a) contacting a test sample with a cell expressing a Peyer's patch or intestinal lymph node-expressed Toll-like receptor". As described above for claim 1, the art (Shimosato et al, 2003) teaches that TLR9 is inherently expressed in Peyer's patch or intestinal lymph node. Thus, the teachings of Akira et al anticipate claim 13 for the same reason as claim 1.

Claim 15 depends from claim 1 and limits the TLR to Toll-like receptor 9 (TLR9). The teachings of Akira et al described above that anticipate claim 1 are directed to TLR9. Thus, Akira et al anticipate claim 15 for the same reason as claim 1.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 and 12-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Lipford et al, WO 2004/026888 (published 1 April 2004, filed 19 September 2003 and claiming priority to 19 September 2002).

Claims 1-5, 12, 13 and 15 are interpreted as described above in the rejection under 35 U.S.C. 102(b).

Claim 1 is anticipated by Lipford et al for the following reasons. Lipford et al teach that TLR9 has "is known to be involved in innate immunity and to signal in response to

CpG DNA" (pg 1). Lipford et al teach that human and murine TLR9 were known in the prior art, and further disclose "novel amino acid and nucleotide sequences of rat, pig, cow, and horse TLR9" (pg 1). Lipford et al further teach that "the invention provides a screening method to identify a TLR9 ligand. The method involves contacting a polypeptide (including a chimeric TLR9 polypeptide) of the invention with a candidate TLR9 ligand; measuring signal in response to the contacting; and identifying the candidate TLR9 signal as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the candidate TLR9 ligand is an immunostimulatory nucleic acid. In one embodiment the candidate TLR9 ligand is a CpG DNA" (pg 5, lines 5-11). Lipford et al further teach that "[a] TLR9 ligand that is an immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell that expresses TLR9". Lipford et al further teach that "[a] basis for certain of the screening assays is the presence of a functional TLR9 in a cell" and that recombinant cells expressing TLR9 are capable of "activating the TLR/IL-1R signaling pathway in response to contact with an immunostimulatory molecule". The corollary to this teaching is that the cells do not activate the signaling pathway if not contacted with an immunostimulatory molecule. Thus, Lipford et al teach selecting a ligand based on an increase an activity as compared to a cell not contacted with a test sample. Thus, Lipford et al teach a method comprising the steps of (a) contacting a test sample (e.g., candidate TLR9 ligand) with a cell expressing a TLR9, and (b) measuring activity of the TLR9 using signal transduction in the cell as an indicator, and wherein a compound is identified by the method if it increases activity of the TLR9 as compared to the activity of the TLR9 in a cell not contacted with the test sample. Thus, the teachings of Lipford et al anticipate claim 1.

Claim 2 is also anticipated by the teachings of Lipford et al for the following reasons. Lipford et al specify that "[i]n one embodiment the screening method is performed on a plurality of test compounds" (page 6). Lipford et al further teach a plurality of compounds to test, including nucleic acids, polypeptides, lipids and small molecules (pg 36, lines 24-26). Furthermore, as described above, Lipford et al teach selection of ligands that activate when in contact with the receptor. The corollary to this

teaching is that the cells do not activate the signaling pathway if not contacted with an immunostimulatory molecule. Thus, Lipford et al teach selecting ligands (including a plurality of ligands) based on an increase an activity as compared to a cell not contacted with a test sample. Thus, the teachings of Lipford et al also anticipate claim 2.

Claim 3 is anticipated by Lipford et al for the following reasons. Lipford et al further teaches that "an isolated nucleic acid … of the invention may be admixed with a pharmaceutically acceptable carrier in a pharmaceutical preparation" (pg 7, lines 16-17). The term "nucleic acid of the invention" encompasses the TLR9 immunostimulatory nucleic acids taught by Lipford et al (described above). Thus, Lipford et al teaches the further step of mixing the sample assessed to activate the receptor with a pharmaceutically acceptable carrier. Thus, the teachings of Lipford et al also anticipate claim 3.

Claim 4 is anticipated by Lipford et al for the following reasons. Lipford et al further teaches that "immunostimulatory nucleic acids useful according to the invention can be obtained from natural sources" including "prokaryotic sources" including being purified from bacterial nucleic acids (pg 33, lines 1-14). Thus, the teachings of Lipford et al also anticipate claim 4.

Claim 5 is anticipated by Lipford et al for the following reasons. As described above for claim 2, Lipford et al teach the use of a plurality of test samples, and as described above for claim 4, Lipford et al teach use of nucleic acids from "prokaryotic sources" (plural). Thus, the teachings of Lipford et al also anticipate claim 5

Claim 12 depends from claim 1 and limits the "intestinal tract tissue" to "intestinal lymphoid tissue". The only recitation of "intestinal tract tissue" in claim 1 is lines 3-4, which recite "...expressing an intestinal tract tissue-expressed Toll like receptor". Thus, claim 12 limits claim 1 to one wherein step (a) is "(a) contacting a test sample with a cell expressing an intestinal lymphoid tissue-expressed Toll-like receptor". As described above for claim 1, the art (Shimosato et al, 2003) teaches that TLR9 is inherently expressed in intestinal lymphoid tissue. Thus, the teachings of Lipford et al anticipate claim 12 for the same reason as claim 1.

Claim 13 depends from claim 12 and limits "intestinal lymphoid tissue" to "Peyer's patch or intestinal lymph node". Thus, claim 13 limits claim 12 to one wherein step (a) is "(a) contacting a test sample with a cell expressing a Peyer's patch or intestinal lymph node-expressed Toll-like receptor". As described above for claim 1, the art (Shimosato et al, 2003) teaches that TLR9 is inherently expressed in Peyer's patch or intestinal lymph node. Thus, the teachings of Lipford et al anticipate claim 13 for the same reason as claim 1.

Claim 14 depends from claim 1 and limits the Toll-like receptor to one from swine (claim 14) or Toll-like receptor 9 (claim 15). The teachings of Lipford et al described above that anticipate claim 1 include the use of swine (porcine) Toll-like receptor 9 (TLR9). Lipford et al disclose a porcine/swine (*Sus scrofa*) TLR9 as SEQ ID NO: 5 (1030 amino acids). Thus, the teachings of Lipford et al anticipate claim 14 for the same reason as claim 1.

Claim 15 depends from claim 1 and limits the TLR to Toll-like receptor 9 (TLR9). The teachings of Lipford et al described above that anticipate claim 1 are directed to TLR9. Thus, Lipford et al anticipate claim 15 for the same reason as claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akira et al, WO 02/06482 (published January 24, 2002; reference F2 on the 7/27/06 IDS; in light of the translation provided by U.S. Patent Application Publication 20030124655) as applied to claim 5 above, and further in view of Kitazawa et al (2003. International Journal of Food Microbiology. 85(1-2):11-21; published 15 August 2003 but available one 16 November 2002; 17 pages as printed).

Claim 6 depends from claim 5. In claim 6, the recitation of “for producing a food composition that activates the intestinal tract immune system” in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Claim 6 additionally recites a "further step of mixing the microorganism assessed to activate the intestinal tract system with a dietarily acceptable carrier". This step does not specify whether the mixing is done prior to or after the assessment steps of claim 5; therefore, claim 6 broadly encompass such mixing prior to or after the assessment takes place.

Furthermore, as with parent claim 5, the limitation of "microorganism assessed to activate the intestinal tract immune system" is met by any microorganism with an extract that activates the Toll-like receptor when practicing the method steps of the claim.

Claim 7 depends from claim 6, and limits the microorganism to a lactic acid bacterium. As described above in the section titled, "Claim Rejections, 35 USC 112, 2nd paragraph", claim 7 is indefinite because the antecedent basis of "microorganism" is not clear. The recitation "microorganism" does not distinguish between the "test microorganisms" and the "those assessed to activate" (as recited in claims 5 and 6). Each genus differs in scope and it is not clear which is referred to in claim 7 by the recitation of "the microorganism". For purposes of prosecution, the claim is interpreted broadly to encompass either possibility.

As described above, Akira et al teaches all of the limitations of claim 5. As noted therein, Akira et al teach that bacterial DNA having an unmethylated CpG sequence can be used in the screening methods for agonists (¶ 54, last sentence).

Akira et al do not teach the additional step of claim 6 wherein a microorganism assessed to activate is mixed with a dietarily acceptable carrier, or the additional limitation of claim 7 that the microorganism (either tested or assessed to activate) is a "lactic acid bacterium".

Kitazawa et al teach (see Title and Abstract) that an immunostimulatory oligonucleotide with a CpG-like motif exists in the yogurt-producing lactic acid bacterium *Lactobacillus delbrueckii ssp. bulgaricus* (also referred to as *L. bulgaricus*). Kitazawa et al further teach (pg 4) culture of said lactic acid bacterium in MRS medium, which is

inherently a dietarily acceptable medium, as evidenced by Duval-Iflah et al (1998. Antonie van Leeuwenhoek. 73: 95-102; cited here solely to support inherency). Duval-Iflah et al fed *L. bulgaricus* in MRS broth directly to mice (pg 97; "[b]acterial MRS cultures were given each day instead of drinking water"), which demonstrates that *L. bulgaricus* in MRS broth is dietarily acceptable.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform the screening method of claim 5 as taught by Akira et al (with bacterial DNA having an unmethylated CpG sequence and a cell expressing a TLR9 receptor), but to substitute an extract (CpG DNA) from the microorganism (*L. bulgaricus*) taught by Kitazawa et al for the extract (CpG DNA) from the microorganism (bacteria in general) taught by Akira et al, and to further mix a microorganism assessed to activate the Toll-like receptor with a dietarily acceptable carrier (MRS broth) taught by Kitazawa et al; said mixing step would be performed both before and after the microorganism is assessed. The person of ordinary skill in the art would be motivated to do so in order to determine if the CpG DNA taught by Kitazawa et al is one of the TLR9 activating CpG sequences taught by Akira et al. The person of ordinary skill in the art would be motivated to mixing the microorganism with a MRS broth because Kitazawa et al exemplify this broth as medium for culturing *L. bulgaricus*; furthermore, the skilled artisan would be motivated to culture this bacteria in this medium both prior to and after assessing the bacteria, as propagating the bacteria requires use of a culturing medium. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the method Akira et al in view of Kitazawa et al because such modification would merely require applying the specific bacteria containing a CpG motif taught by Kitazawa et al to the general method taught by Akira et al, and further culturing the bacteria as exemplified by Kitazawa et al.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al, WO 2004/026888 (published 1 April 2004, filed 19 September 2003 and claiming priority to 19 September 2002) as applied to claim 5 above, and further in view

of Kitazawa et al (2003. International Journal of Food Microbiology. 85(1-2):11-21; published 15 August 2003 but available one 16 November 2002; 17 pages as printed).

Claims 6 and 7 are interpreted as described above.

As described above, Lipford et al teaches all of the limitations of claim 5. Lipford et al further teach that the candidate ligand to be tested can be CpG DNA (pg 5, line 11), which is an extract (nucleic acid) from a microorganism (bacterial).

Lipford et al do not teach the additional step of claim 6 wherein a microorganism assessed to activate is mixed with a dietarily acceptable carrier. Lipford et al do not teach the additional limitation of claim 7 that the microorganism (either tested or assessed to activate) is a "lactic acid bacterium".

Kitazawa et al teach (see Title and Abstract) that an immunostimulatory oligonucleotide with a CpG-like motif exists in the yogurt-producing lactic acid bacterium *Lactobacillus delbrueckii ssp. bulgaricus* (also referred to as *L. bulgaricus*). Kitazawa et al further teach (pg 4) culture of said lactic acid bacterium in MRS medium, which is inherently a dietarily acceptable medium, as evidenced by Duval-Iflah et al (1998. Antonie van Leeuwenhoek. 73: 95-102; cited here solely to support inherency). Duval-Iflah et al fed *L. bulgaricus* in MRS broth directly to mice (pg 97; "Bacterial MRS cultures were given each day instead of drinking water"), which demonstrates that *L. bulgaricus* in MRS broth is dietarily acceptable.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform the screening method of claim 5 as taught by Lipford et al (with an extract from a microorganism and a cell expressing a TLR9 receptor), but to substitute an extract (CpG DNA) from the microorganism (*L. bulgaricus*) taught by Kitazawa et al for the extract (CpG DNA) from the microorganism (bacteria in general) taught by Lipford et al, and to further mix a microorganism assessed to activate the Toll-like receptor with a dietarily acceptable carrier (MRS broth) taught by Kitazawa et al; said mixing step would be performed both before and after the microorganism is assessed. The person of ordinary skill in the art would be motivated to do so in order to determine if the CpG DNA taught by Kitazawa et al is one of the TLR9 activating CpG sequences taught by Lipford et al. The person of ordinary skill in the art would be

motivated to mixing the microorganism with a MRS broth because Kitazawa et al exemplify this broth as medium for culturing *L. bulgaricus*; furthermore, the skilled artisan would be motivated to culture this bacteria in this medium both prior to and after assessing the bacteria, as propagating the bacteria requires use of a culturing medium. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success in modifying the method Lipford et al in view of Kitazawa et al because such modification would merely require applying the specific bacteria containing a CpG motif taught by Kitazawa et al to the general method taught by Lipford et al, and further culturing the bacteria as exemplified by Kitazawa et al.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647